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Metabolic Imaging of Brain Tumor by ^{99m}Tc-Tetrofosmin Scintitomography

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1. Introduction

Primary brain tumors have an annual incidence rate ranging between 7 and 19 new cases per 100,000 population. Metastatic tumors to the brain are more common, with more than 100,000 patients per year in the United States. Gliomas are the most common primary brain tumors (DeAngelis, 2001). Among them, astrocytomas account for more than half of all primary malignancies of the central nervous system (CNS). They are classified into 4 grades: Grades I and II are considered as low-grade; anaplastic tumors (Grade III) and glioblastoma multiforme (Grade IV) are considered high-grade tumors.

Glioblastoma multiforme (GBM) is the most common and most malignant of the glial tumors occurring in adults (Liu et al., 2010). Other types are oligodendrogliomas, ependymomas, meningiomas, pituitary adenomas, embryonal tumors and gangliogliomas. Among them meningiomas are the most common benign intracranial tumors, accounting for up to one fourth of all primary lesions (Whittle et al., 2004). The most common presenting symptoms of brain tumors are due to increased intracranial pressure (headache, nausea, vomiting), seizures, focal neurological deficits and possibly cognitive deterioration.

With regards to treatment, in low-grade lesions radical surgical removal will generally allow functional survival for many years. Adjuvant radiotherapy can halt disease progress for a time and probably increases survival. For high-grade tumors surgical resection is almost always followed by radiotherapy and adjuvant chemotherapy that are usually given concomitantly. Temozolomide is the mainstay of treatment administered in parallel with and post-radiotherapy, with benefits in overall survival (Stupp et al., 2005). Patients younger than 60 years, with good functional status and gross total tumor resection have a better prognosis (Scott et al., 1999).

Computed tomography (CT) and magnetic resonance imaging (MRI) are necessary to characterize gross tumor appearance, size and extension. Nevertheless, in patients with brain lesions it is not uncommon for radiomorphological modalities to provide non-specific information, even after infusion of iodine-based contrast media or gadolinium-based paramagnetic complexes. An enhancing lesion may represent a glioma, an abscess, a metastasis or even a primary CNS lymphoma.

To gain additional diagnostic information from that acquired by conventional radiology, functional metabolic imaging by nuclear medicine techniques has been introduced, aiming to provide information related to the metabolic status of brain tumors. These metabolic

imaging modalities comprise single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Although PET may be credited with providing the impetus for the new clinical interest in functional neuroimaging, SPECT has offered a credible alternative with the advantage of lower cost and wider availability.

Various single-photon emitting radiotracers have been used to date, thallium-201 (^{201}Tl) being among the first and mostly studied. Technetium-99m (^{99m}Tc)-labeled compounds have also been evaluated, including ^{99m}Tc-methionine, ^{99m}Tc-glucoheptonate and more extensively ^{99m}Tc-hexakis-2-methoxy isobutyl isonitrile (^{99m}Tc-sestamibi or ^{99m}Tc-MIBI). For a number of reasons including higher photon flux, better spatial resolution, less radiation burden to the patient and excellent availability, the use of ^{99m}Tc-based compounds has progressively prevailed over ^{201}Tl.

^{99m}Tc-tetrofosmin (^{99m}Tc-TF) is another ^{99m}Tc-based SPECT radiotracer that demonstrates certain similarities with ^{99m}Tc-MIBI. Both are routinely used for myocardial perfusion imaging, but also exhibit tumor-seeking properties. Whereas ^{99m}Tc-MIBI has been extensively evaluated in imaging brain tumors for nearly two decades, ^{99m}Tc-TF has been introduced in this field for a considerably shorter period of time.

2. The radiotracer and its cellular uptake mechanism

^{99m}Tc-TF is a lipophilic cationic diphosphine routinely used for myocardial perfusion imaging and has also been shown to exhibit certain tumor-seeking properties. These properties have been verified in various neoplasms including parathyroid adenoma and several carcinomas (e.g. of the breast, thyroid, nasopharynx and lung). Its uptake by intracranial tumors is under meticulous investigation during the past few years.

After intravenous administration, the tracer reaches the brain by the arterial blood flow. Despite being a lipophilic molecule, ^{99m}Tc-TF cannot cross the intact blood-brain barrier (BBB), which results in negligible tracer uptake in the healthy brain parenchyma. There is, however, some tracer accumulation normally occurring in the choroid plexuses and the pituitary gland, brain structures that lack BBB.

In order for ^{99m}Tc-TF to be taken up by the cells of a brain lesion, this has to disrupt the BBB. Its uptake mechanism depends on the blood flow to the lesion, as well as on the integrity of the membrane of the lesion cells, an indicator of their viability. The tracer enters viable cells mainly via passive transport, driven by the negative electric potential of the intact cell membrane, and it mostly localizes within the cytosol, with only a fraction passing into the mitochondria. In that sense, cellular ^{99m}Tc-TF uptake mainly reflects on the viability of lesion cells and their metabolic status.

As discussed in the following paragraphs, initial clinical evidence from *in vivo* studies suggests that there is a significant correlation between tracer uptake and cellular proliferation in both gliomas and meningiomas (Alexiou et al., 2008a, 2008b; Fotopoulos et al., 2008). Cellular proliferative activity may thus be regarded as a major driving force that leads to significant intracellular tracer accumulation and retention.

Other studies on human glioma cell lines *in vitro* and *in vivo* revealed that ^{99m}Tc-TF is influenced to a very small degree by the expression of P-glycoprotein (P-gp) (Le Jeune et al., 2005; Alexiou et al., 2011). P-gp is a membrane protein encoded by the multi-drug resistance (MDR) gene and acts as an ATP-dependent drug efflux pump, excreting anticancer pharmaceuticals and radiopharmaceutical imaging agents outside the tumor cell. Although both ^{99m}Tc-TF and ^{99m}Tc-MIBI have been found *in vitro* to be substrates of P-gp, the fact that

^{99m}Tc-TF uptake in glioma cells is not particularly influenced by the expression of their MDR protein genotype substantiates a plausible clinical superiority over ^{99m}Tc-MIBI, which is prone to extracellular excretion by P-gp.

3. Protocol of brain SPECT imaging

The radiopharmaceutical is prepared in the nuclear medicine department with the use of a commercially available powder kit (Myoview™, General Electric Healthcare Ltd., Buckinghamshire, UK), which is reconstituted with freshly eluted ^{99m}Tc pertechnetate ($^{99m}TcO_4^-$) sterile solution. Comparison of ^{99m}Tc-TF uptake in various types of lesions during imaging performed consecutively at 20, 40 and 120 min post-injection did not reveal any considerable fluctuations of relative tracer uptake over time (Soricelli et al., 1998). Hence, image acquisition at 20–30 min after radiotracer administration can be safely adopted as a convenient rule of thumb. The radiopharmaceutical is injected intravenously, at an administered activity of approximately 740-925 MBq (20-25 mCi).

All SPECT studies in our department are implemented on the same dual-head γ-camera (Millennium™ VG3, General Electric Medical Systems – Europe, Buc Cedex, France), equipped with a pair of low-energy, high-resolution, parallel-hole collimators. The matrix is set at 128 × 128 pixels; the photopeak is centered at 140 keV, allowing a symmetrical 10% window. The tomographic imaging parameters consist of a full-circle (360°) rotation angle, a 3°-step-and-shoot technique and an acquisition time of 30 sec per frame. Raw imaging data are reconstructed using the Butterworth-filtered back-projection algorithm (critical frequency [order]: 0.25; filter power: 5.0), generating tomographic views of the brain in the three planes (transverse, coronal and sagittal). In the case of γ-cameras with an integrated computed tomograph (hybrid SPECT/CT systems), data from a low-dose CT scan can be used for attenuation correction of the scintigraphic image. In non-hybrid modalities — currently comprising the vast majority— attenuation correction can be applied empirically during tomographic image reconstruction following the Chang method (attenuation factor: 0.11/cm).

3.1 Image analysis and interpretation

Radiotracer uptake in the brain is first assessed visually. ^{99m}Tc-TF cannot penetrate the intact BBB and does not accumulate in the normal brain parenchyma, so any abnormal uptake is readily identifiable against the negligible normal-brain background. Exceptions to this are the choroid plexuses and the pituitary, structures that lack BBB so they normally accumulate an amount of the tracer (Fig. 1). Space-occupying lesions adjacent to these structures could face obvious limitations in delineating their true scintigraphic margins and estimate the tracer uptake that is attributable to the lesion *per se*.

Semi-automated, semi-quantitative image analysis is a valuable adjunct to the objective visual image reading and adds subjectivity to the interpretation of the study. It is applied on the reconstructed SPECT images by calculating the lesion-to-normal (L/N) ratio of relative radiotracer uptake —hence the term 'semi-quantitative'. In our department the transversal SPECT slice in which lesion tracer uptake appears to be maximal is chosen manually — hence the term 'semi-automated'. This is performed in close reference to the corresponding CT/MRI transversal slices that serve as a reference guide of the lesion's topography.

After the selection of the slice with maximal lesion uptake, relative tracer concentration is calculated with the use of the Java-based, open-source image processing software *ImageJ*

(http://rsb.info.nih.gov/ij/index.html), developed by the National Institutes of Health. A region of interest (ROI) encircling the lesion is defined manually on the selected transversal slice and a second identical (mirror) region is drawn on the contra lateral normal side of the brain (Fig. 2). The L/N ratio is calculated by dividing the average counts in the lesion ROI by those in the contra lateral (background) ROI. The ROIs are independently evaluated for eligibility by two experienced nuclear medicine physicians and possible disagreements are resolved by consensus.

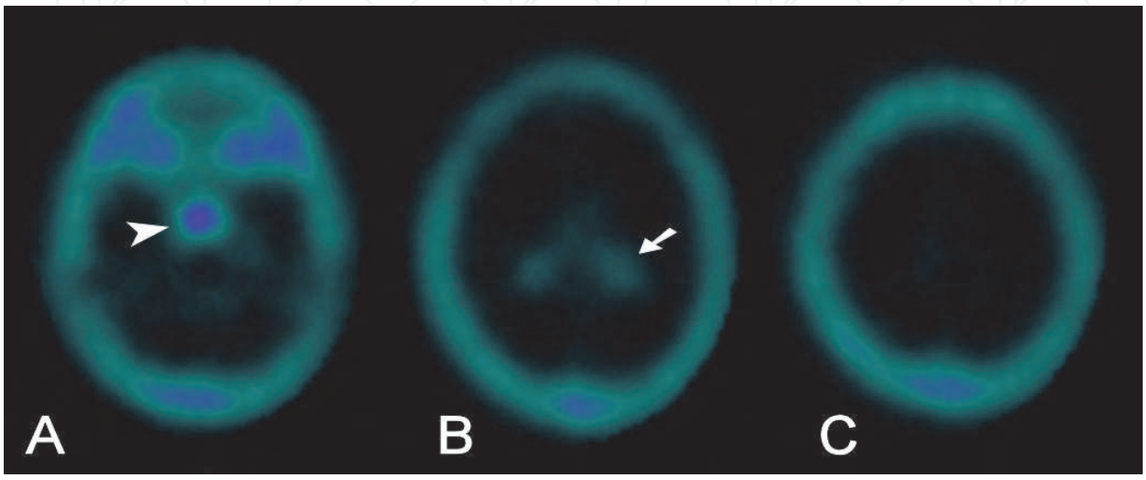


Fig. 1. A normal ^{99m}Tc-tetrofosmin brain SPECT study (transversal slicing in three different planes) displaying physiological tracer accumulation in the choroid plexuses (arrow), the pituitary (arrowhead) and the scalp.

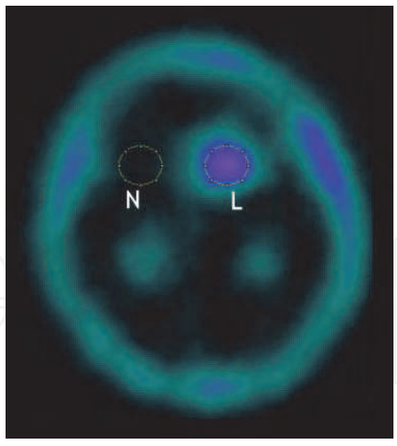


Fig. 2. ROI definition over the lesion (L) and over the normal brain parenchyma (N).

The application of the above methodology for L/N ratio calculation in everyday clinical practice is, in most cases, a straightforward process that provides reproducible results without significant deviations. Nevertheless, the location of the lesion within the brain and its morphology are critical factors for the application and effectiveness of the proposed technique. Lesion adjacency to anatomical structures with normal tracer uptake (choroid plexus, pituitary) increases the difficulty of reliable L/N calculation and the chances of its

overestimation. In such cases, the operator has to make sure that the lesion ROI avoids normal structure uptake and encompasses only areas unquestionably pathologic, even if these do not appear to exhibit the maximum intensity of relative tracer uptake. Heterogeneity of tracer distribution within a lesion (e.g. due to local necrosis) may impose L/N calculation in more than one areas/SPECT slices. When large variations in tracer uptake intensity are apparent, a tight ROI around the highest uptake region may be more reliable than a looser one, which could lead to L/N underestimation. For lesions located around the midline there may not be a definite mirror area to draw the normal ROI; a nearby site could be safely selected in the majority of similar cases, since the level of the background activity is generally very low throughout.

4. Clinical applications

Our experience thus far with ^{99m}Tc-TF is based on its clinical use in SPECT imaging studies performed in nearly 200 cases of space-occupying brain lesions. Obtained results to date conform to the fact that ^{99m}Tc-TF brain SPECT can contribute substantial functional information to the structural data already obtained by CT and conventional MRI, thus helping to establish non-invasively an accurate diagnosis. Furthermore, based on observations in patients with high-grade gliomas, it looks like this radiotracer also carries a plausible prognostic role that merits further investigation.

In the following paragraphs the discussion will focus on the experience gained so far by the use of ^{99m}Tc-TF SPECT in the management of patients treated for brain tumor; the role of other SPECT and PET radiotracers and of other CNS imaging modalities such as conventional and functional MRI will also be mentioned.

4.1 Evaluation of intracranial space-occupying lesions: differentiation of high-grade from low-grade gliomas and non-neoplastic pathologies

Differentiating neoplastic from non-neoplastic intra-axial lesions is of paramount importance for patient management. Neoplastic and non-neoplastic pathologies may equally produce abnormal contrast enhancement, mass effects and perilesional edema on CT and classic MRI (Al-Okaili et al., 2007). Consequently, such clinical situations often constitute a diagnostic dilemma and it is not uncommon to seek the help of histological verification to establish a diagnosis.

The data of a prospectively implemented study comprising 106 patients hospitalized in the neurosurgery department of our institution over a 5-year period (between September 2004 and September 2009) were analyzed recently; all cases have been submitted to surgery due to an intracranial lesion suspicious of tumor on conventional radiological imaging. The patients underwent ^{99m}Tc-TF brain SPECT within a 7-10 day period after radiological diagnosis, with surgery following shortly after SPECT to establish histologically the final diagnosis. The only cases that did not receive surgery were among previously treated tumors resubmitted owning to suspected recurrence. These individuals were closely followed-up clinically and radiologically over a period of 6 months, to verify stability suggestive of radionecrosis, or on the other hand, disease progression consistent with tumor relapse.

Ninety patients suffered from neoplastic lesions and 16 harbored non-neoplastic pathologies (abscesses, non-malignant hemorrhages, radiation necroses). ^{99m}Tc-TF was taken up more

avidly by high-grade gliomas (Fig. 3) than by low-grade lesions and could reliably distinguish them, with an L/N ratio of 2.8 providing the optimal discrimination threshold (Fotopoulos et al., 2011). Similar findings have also been reported by other authors (Choi et al., 2000). Furthermore, ^{99m}Tc-TF differentiated effectively high- and low-grade gliomas from non-neoplastic lesions. Nonetheless, differentiation between gliomas between gliomas — either low- or high-grade— and metastases was not feasible on the basis of scintigraphic (L/N) criteria.

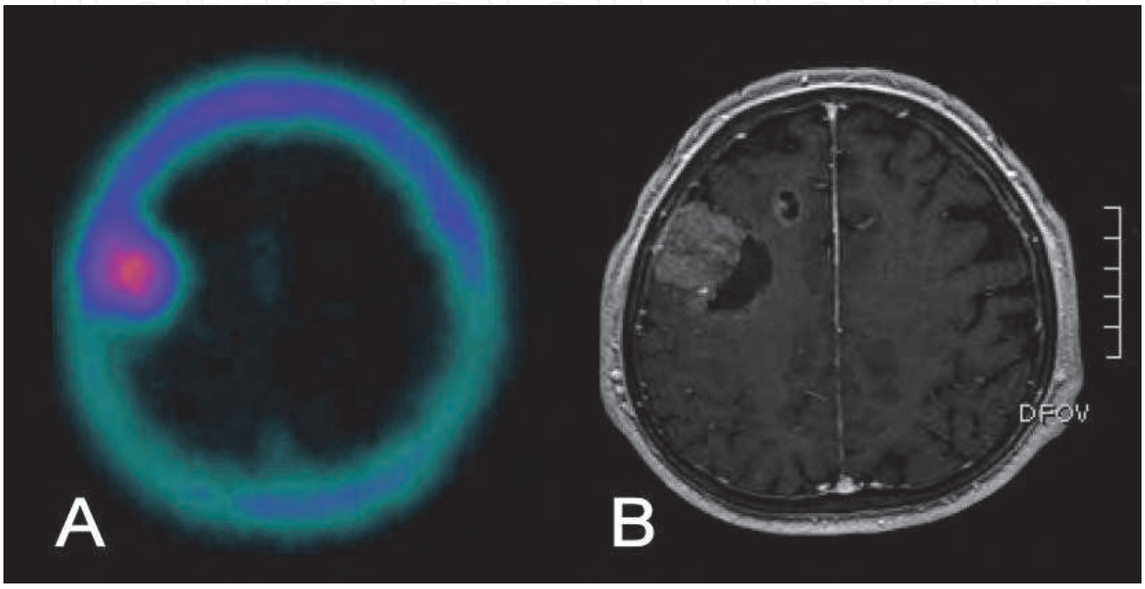


Fig. 3. High-grade glioma associated with significant tracer uptake (L/N=16).

Several other SPECT tracers have been used for the initial evaluation of brain lesions. ^{201}Tl was able to differentiate malignant tumors from poorly vascularized benign lesions, yet faced a limited ability to separate between the latter and low-grade astrocytomas, as well as tumors from abscesses (Staffen et al., 1998; Kinuya et al., 2002). ^{99m}Tc-MIBI has been evaluated in various brain pathologies. If performed within 5 days of symptom onset, it has been found capable of differentiating neoplastic from non-neoplastic intracerebral hematomas (Minutoli et al., 2005). Iodine-123-α-methyl tyrosine (^{123}I-IMT) was also among the SPECT tracers to provide encouraging results for imaging tumor recurrence (Samnick et al., 2002).

4.1.1 Discriminating recurrent disease from radiation necrosis in previously treated tumors

Treatment of brain gliomas depends on their localisation, cell type and grade of malignancy. It normally combines surgery, radiation therapy and chemotherapy. Radiotherapy —in the form of external beam radiation, brachytherapy, or stereotactic radiotherapy— consists the primary adjuvant treatment after surgical resection. Among the delayed side effects of radiation therapy, radionecrosis is the most prominent, primarily depending on the administered dose and rate of delivery and usually occurs within 6 months to 2 years, the same period during which disease recurrence is also rather frequent (Marks & Wong, 1985).

Radiation injury is usually localized around the tumor bed umor bed —where recurrent glioma is also typically located—, although occasional reports describe necrosis arising anywhere in the path of the irradiation beam. It is not uncommon for radiation injury and recurrent disease to coexist.

Since these two entities have diverse treatment approach and prognosis, differentiation between them is crucial and several imaging techniques have been evaluated towards this objective. Morphological depiction of the brain by classic MRI and CT can merely recognize edema and BBB disruption, so it is usually inconclusive and faces inherent limitations in discriminating viable tumor from post-irradiation change (Byrne, 1994).

Depiction of recurrent tumor was the first imaging challenge against which we evaluated ^{99m}Tc-TF brain SPECT accuracy a few years back (Alexiou et al., 2007). A prospective ongoing study enrolled 24 patients that had been previously treated surgically for brain tumor followed by external beam radiotherapy, while some had also received adjuvant chemotherapy. No residual tumor had been recognized on radiological imaging immediately after initial treatment. On follow-up they developed neurological symptomatology consistent with tumor recurrence, with radiological investigation verifying the presence of a contrast-enhancing lesion with edema and mass effects. In 5 cases surgical excision of the lesion was performed within a week after ^{99m}Tc-TF scintigraphy and a diagnosis was reached histologically. In the rest the diagnosis was based on clinical and neuromorphological follow-up, owning to various reasons (technically inoperable lesions, critical clinical condition, patient refusal to re-operate etc.). A 6-month 'wait-and-see' period is considered sufficient by most to reach a safe estimation of the diagnosis. This is because by that time glioma growth within the limited space of the cranial cavity will definitelly result in clinical deterioration and radiological progression, which may safely be considered as indicative of recurrence.

On tumor recurrence SPECT depicted increased ^{99m}Tc-TF uptake in the region of the brain that corresponded to the radiologically detected lesion, suggesting the presence of viable hypermetabolic tissue (Fig. 4). On the contrary, radionecrotic lesions tended to exhibit significantly fainter tracer uptake (Fig. 5). Receiver operating characteristic (ROC) curve statistical analysis returned a threshold L/N value of 4.8 as most accurately discriminating these two clinical entities. However, it must be kept in mind that, according to relevant reports, ^{99m}Tc-TF SPECT exhibits suboptimal sensitivity in detecting recurrence of tumors located subtentorially in the posterior fossa (Barai et al., 2003).

^{201}Tl was one of the first single-photon emitting radiotracers evaluated in the same clinical setting. Published data thus far suggest a wide range of sensitivity and specificity in detecting tumor recurrence in patients with previously treated supratentorial gliomas, partially owning to varying occurrence of false positives; still ^{201}Tl SPECT is reported to have an advantage over conventional MRI (Vos et al., 2007). ^{99m}Tc-MIBI has also been extensively evaluated with good reported results and a significant diagnostic advantage over contrast-enhanced MRI (Soler et al., 1998). Imaging protein synthesis using radiolabeled amino acids is another approach employed towards non-invasive revelation of tumor recurrence. Various natural amino acids have been labeled with radioactive isotopes —mostly PET— and are currently investigated. As regards SPECT, encouraging results were reported for ^{99m}Tc-methionine and ^{123}I-IMT (Barai et al., 2004; Samnick et al., 2002).

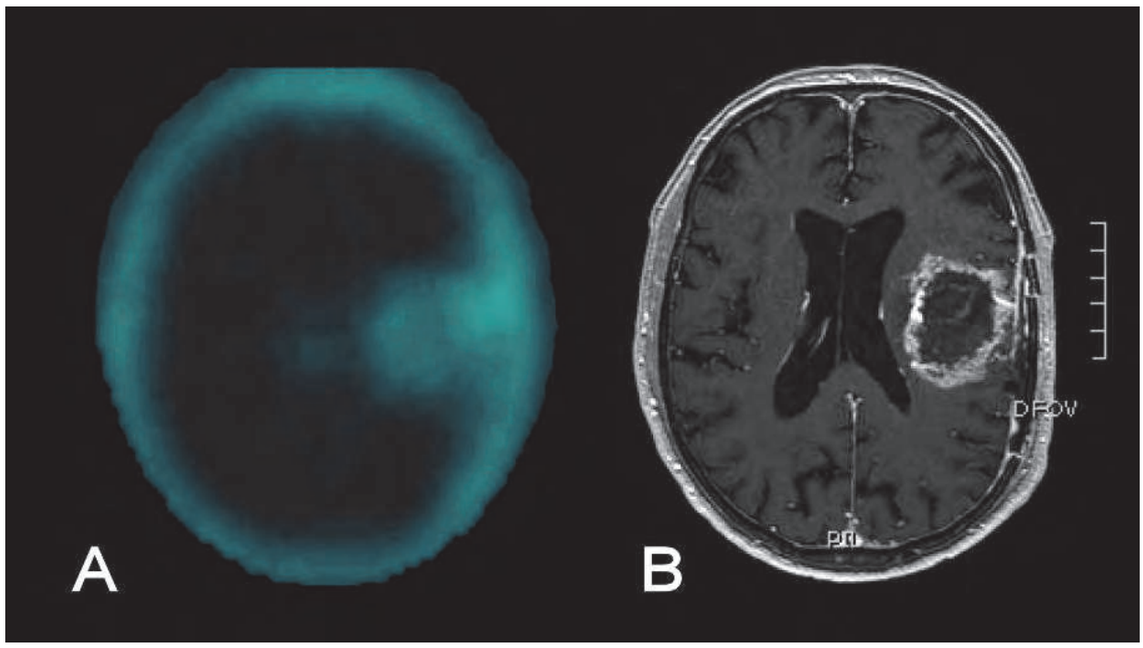


Fig. 4. Recurrent astrocytoma characterized by intense tracer uptake (L/N=8.7).

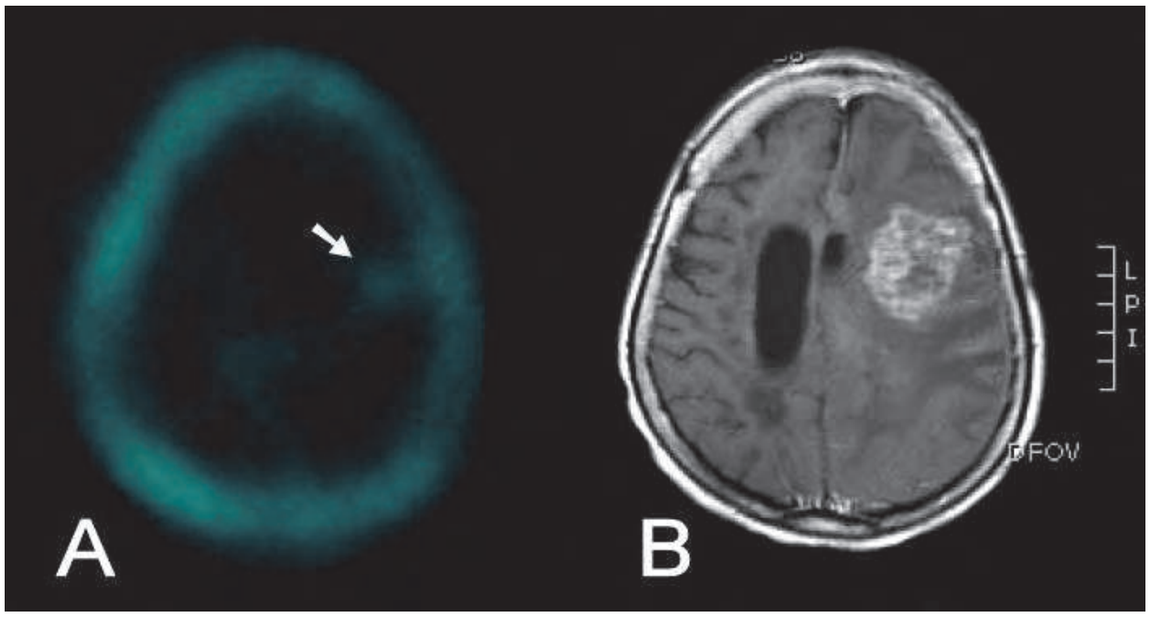


Fig. 5. Radiation necrosis exhibiting only mildly increased tracer uptake (L/N=2.9).

4.1.2 Spontaneous intracerebral hemorrhage: Masking an underlying neoplasm?

With reference to non-traumatic intracerebral hemorrhage (ICH), distinguishing a neoplastic from a non-neoplastic one constitutes a challenging task, since neoplasms can be hidden behind an intracerebral hematoma, while some non-neoplastic hemorrhages may mimic neoplasms on standard radiomorphological imaging. Bleeding deriving from a malignant brain lesion accounts for approximately 10% of all ICHs, with metastases displaying the

highest susceptibility. The pre-operative diagnosis of a tumor as the underlying cause of an ICH is usually very difficult for CT and MRI, even for the modern functional MRI techniques. Hence diagnosis is based on evolution patterns of the hematoma in a series of sequential radiological studies over a period of several weeks, until the extravasated blood is absorbed so the tumor revealed.

^{99m}Tc-TF SPECT can play a role in differentiating neoplastic from non-neoplastic hemorrhages, since only the latter exhibit negligible to no radiotracer uptake (Alexiou et al., 2006) (Fig. 6). Our experience is based on an increasing series of patients with spontaneous ICH referred to our department, most of whom bear some kind of malignancy. Out of the 8 cases reviewed so far, in half the diagnosis was based on surgery and on a 'wait-and-see' clinical and morphologic follow-up in the rest. Although only two hemorrhages were finally proven to be of neoplastic origin, ^{99m}Tc-TF SPECT managed to accurately identify both (Fotopoulos et al., 2011).

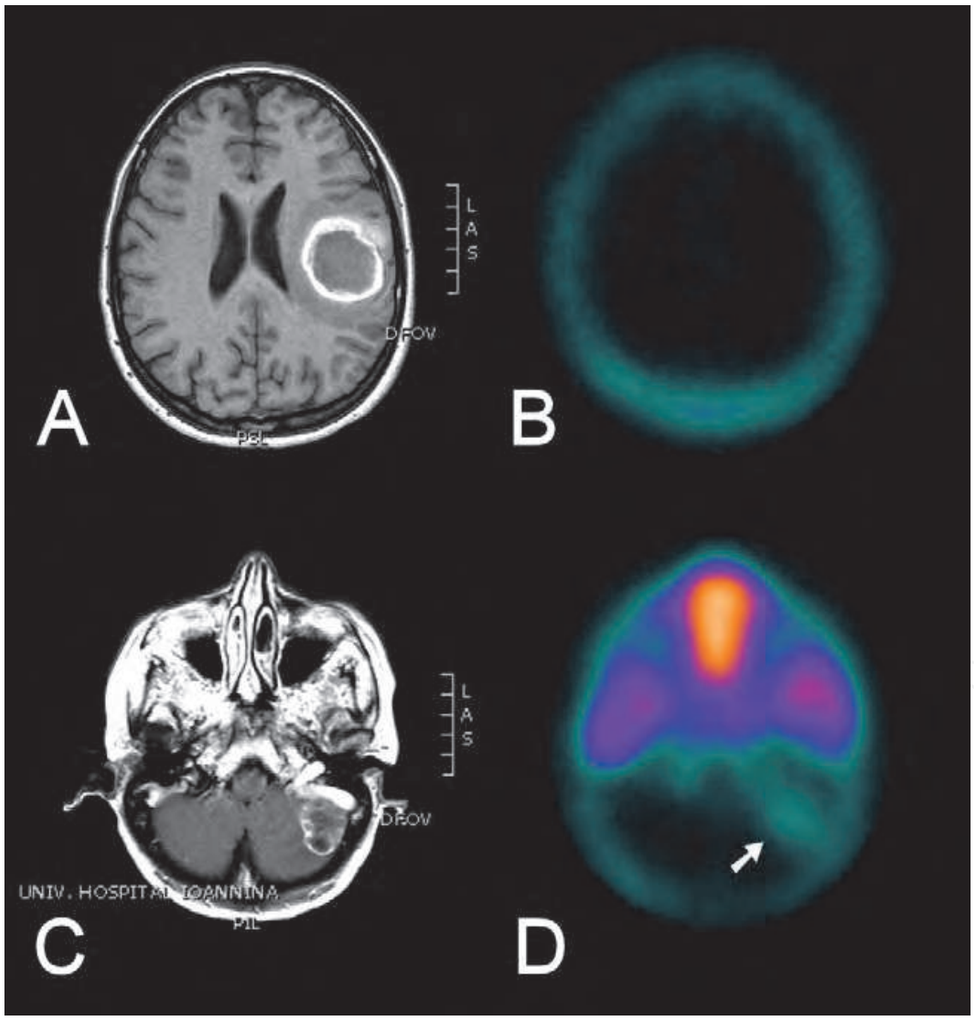


Fig. 6. Intracerebral hemorrhage without signs of tracer uptake, suggesting a benign origin (A, B). On the other hand, a cerebellar hemorrhage exhibits significant tracer uptake (arrow), strongly suggesting the presence of an underlying neoplasm (C, D).

4.2 Assessment of glioma aggressiveness

Assessing the proliferative potential of tumor cells is of paramount importance for predicting their biological behavior, response to therapy and prognosis. Proliferation is equally important in gliomas, since patients with the same histopathological profile that receive equivalent treatment may display diverse natural history and prognosis, owning to differences in the proliferative potential of their disease.

As a result, various methodologies and immunohistological markers have been developed to estimate proliferation in tissue samples. MIB-1 antibody immunostaining to the nuclear antigen Ki-67 is performed routinely and is considered as the most reliable proliferation index, since it is expressed in nearly all phases of the cell cycle, with the exception of phase G_0 (McKeever et al., 1997). Flow cytometry assessing DNA ploidy and S-phase fraction can also provide reliable clues on glioma aggressiveness (Garcia et al., 1997). Nevertheless, these methods require tissue sampling through biopsy or over the course of a surgical procedure. It is therefore equally important for functional imaging to develop radiolabeled tracers that can provide non-invasively an accurate *in vivo* estimate of glioma proliferation.

In a prospective pilot study we evaluated the relationship between glioma proliferation, as expressed by the Ki-67 immunohistological index, and ^{99m}Tc-TF uptake. Patients bearing space-occupying lesions suspicious of glioma on structural brain imaging were enrolled. Within a week after SPECT imaging the lesion was removed surgically and Ki-67 was assessed in the excised specimens. The diagnosed tumors were glioblastoma multiforme (6 cases), anaplastic astrocytoma (1), anaplastic oligodendroglioma (2), low-grade oligodendroglioma (1), and low-grade astrocytoma (1). Statistical analysis revealed a strong positive linear correlation between L/N tracer uptake ratio and Ki-67 expression (Alexiou et al., 2008a). These initial results were supported by another prospective study to follow, in which we sought for a possible correlation between ^{99m}Tc-TF uptake and glioma proliferative activity assessed by flow cytometry. Again, a significant positive linear correlation between radiotracer uptake and the fraction of tumor cells on the S-phase of the cell cycle was verified (Alexiou et al., 2008b).

As regards other SPECT radiotracers, ^{201}Tl was one of the first studied. Reports described a correlation with bromodeoxyuridine (BrdU) and proliferating cell nuclear antigen (PCNA) tissue labeling indices (Oriuchi et al., 1993; Ishibashi et al., 1995; Gungor et al., 2000). ^{99m}Tc-MIBI was found to display a positive correlation with glioma proliferation, as assessed by both flow cytometry and Ki-67, and this was stronger compared to ^{201}Tl (Ak et al., 2003; Nagamachi et al., 2001). With regards to labeled amino acid SPECT, ^{123}I-IMT was similarly reported to correlate with Ki-67 expression (Kuwert et al., 1997). Finally, pentavalent ^{99m}Tc-dimercapto-succinic acid (^{99m}Tc-[V]DMSA) is another tumor-seeking tracer whose proliferative imaging potential in gliomas has been suggested *in vitro* and sporadically reported *in vivo* (Denoyer et al., 2005; Tsiouris et al., 2007).

4.3 Assessment of meningiomas: differentiation between typical and anaplastic and estimation of aggressiveness

Meningiomas account for nearly 30% of all intracranial tumors and are usually diagnosed after the third decade of life, being twice more frequent in women. According to the World Health Organization (WHO) they are classified into benign (grade I), atypical (grade II) and anaplastic/malignant (grade III) (Lamszus, 2004). Although they usually have a relatively benign clinical course and only a 15% recurrence rate, atypical and malignant lesions are associated with high recurrence rates and poor outcome (Kayaselcuk et al., 2004). Their

proliferative potential is essential for their biological characterization, which affects patient management and has prognostic implications. Hence, similarly to gliomas, their non-invasive metabolic characterization constitutes a major objective for CNS imaging.

As with gliomas, we investigated prospectively whether ^{99m}Tc-TF SPECT can provide useful clues for meningioma grade and cellular proliferative activity. After radiomorphological imaging revealed the lesion, scintigraphic imaging by ^{99m}Tc-TF was performed within a week before surgical excision and the surgical specimens were graded following the WHO criteria and stained for Ki-67. The intensity of tumoral radiotracer uptake ranged from restrained to prominent. Malignant lesions tended to exhibit a significantly higher uptake compared to lesions of low histological grade. ROC analysis provided an L/N ratio value of 9.6 as the optimal cut-off point thresholding the two groups. L/N tracer uptake analysis also revealed a significant linear correlation with both meningioma grade and Ki-67 expression (Fotopoulos et al., 2008). These findings pertaining to Ki-67 were sustained by another study, which aimed to correlate meningioma tracer uptake with its proliferative profile, as assessed by flow cytometry. Result analysis revealed a significant correlation of ^{99m}Tc-TF uptake with both the S-phase fraction and the level of DNA aneuploidy (Alexiou et al., 2008b).

^{201}Tl was among the first single-photon emitting radiotracers studied in meningioma. Its uptake pre-operatively has been proposed to differentiate meningiomas with different biological behaviors, while tracer retention by a lesion correlated with its malignant potential (Jinnouchi et al., 1993; Tedeschi et al., 1996). Nevertheless, later reports did not verify any correlation between ^{201}Tl uptake and PCNA labeling index in meningiomas, dissimilar to gliomas (Gungor et al., 2000).

4.4 Patient prognosis

Glioblastoma is the most common and most malignant of the glial tumors occurring in adults, with unfavorable prognosis. Even so, a subset of patients demonstrates long-term survival reaching or even exceeding three years. Since no reliable biomarker has been established for use in clinical practice, prognostic factors already proposed are age at diagnosis, the Karnofsky Performance Score (KPS) and extent of surgical resection, although these inadequately predict outcome (Scott et al., 1999; Lacroix et al., 2001). Identification of solid prognostic variables could recognize patients that may benefit from aggressive treatment schemes and allow for the selection of more homogenous populations in clinical trials.

The correlation between *in vivo* ^{99m}Tc-TF uptake and glioma proliferation, as assessed by the Ki-67 index and flow cytometry, has already been described (Alexiou et al., 2008a, 2008b). Due to the established prognostic value of Ki-67 in gliomas, investigating a possible association between pre-treatment tumoral tracer uptake and overall survival seemed as the next logical step. We followed-up 18 newly diagnosed GBM cases who had been submitted to ^{99m}Tc-TF SPECT prior to surgery. All patients received post-operative standard radiotherapy (6000 rads) with adjuvant temozolomide chemotherapy and then temozolomide up to a year after surgery, or until recurrence. Cases of tumor recurrence were treated by supportive care, with no additional surgery or chemotherapy. Patients bearing lesions with radiotracer L/N uptake 4.7 or less exhibited significantly better survival compared to those with a ratio exceeding 4.7. KPS exceeding 90 was also associated with a better course. Patients with near-total resection or aged under 60 displayed a longer survival trend, although not statistically significant. Multivariate analysis similarly proved

radiotracer uptake and KPS as the only variables with independent prognostic power (Alexiou et al., 2010).
The prognostic value of tumoral ^{201}Tl uptake has been evaluated in the same clinical context and was found associated with worse survival for lesions located supratentorially (Oriuchi et al., 1993). Post-treatment ^{99m}Tc-MIBI uptake has also been described to exhibit prognostic implications in high-grade gliomas and similar results were also reported for ^{123}I-IMT (Beauchesne et al., 2004; Weber et al., 2001).

5. Other metabolic imaging modalities: PET

Brain PET imaging is extensively evaluated towards the distinction between tumors and non-neoplastic brain lesions. Although initial results for fluorine-18 fluoro-deoxyglucose (^{18}F-FDG) PET were encouraging, later studies revealed considerable limitations and, for that reason, other positron-emitting radiotracers were put under perspective (Ricci et al., 1998). Carbon-11 methionine (^{11}C-MET) gave promising results, yet it suffers limited availability owning to the need of an on-site cyclotron to produce the short-lived ^{11}C (Galldiks et al., 2010). ^{18}F-fluoro-choline, O-(2-[^{18}F]fluoro-ethyl)-L-tyrosine (^{18}F-FET) and 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine (^{18}F-FDOPA) are PET tracers that have been proven superior to ^{18}F-FDG for brain tumor imaging (Kwee et al., 2007; Pauleit et al., 2009; Chen et al., 2006).
Diagnosis of brain tumor recurrence has been an imaging challenge also for PET. Although initial reports for ^{18}F-FDG were encouraging (Di Chiro et al., 1988), more recent studies questioned its diagnostic accuracy, which was found considerably inferior to that of ^{201}Tl SPECT in several series (Kahn et al., 1994; Gómez-Río et al., 2008). A significant disadvantage of ^{18}F-FDG derives from its physiological uptake in the glucose-metabolizing normal brain. For that reason other tumor-seeking positron-emitting radiotracers have been developed. ^{11}C-MET PET has given superior results compared to ^{18}F-FDG because of its sensitivity and clearer delineation of recurrence (Van Laere et al., 2005), yet suffers limited availability due to the need of an on-site cyclotron to produce ^{11}C and the same applies for ^{13}N-NH_3 (ammonia), which has also been tried (Xiangsong et al., 2006). Perhaps the most promising PET tracers to date are the labeled analogues of thymidine, 3'-deoxy-3'-^{18}F-fluoro-thymidine (^{18}F-FLT) and of tyrosine, ^{18}F-FET. Their greatest advantage compared to other PET tracers lies in their low uptake by normal brain parenchyma, thus providing a better contrast between tumor and normal brain. Initial experience gained from a series of studies suggests that these agents are superior to ^{18}F-FDG and to conventional MRI in distinguishing tumor recurrence from radiation-induced brain injury (Chen et al., 2005; Pöpperl et al., 2004).
PET has been widely utilized to evaluate glioma proliferation. The uptake kinetics of ^{18}F-FDG reflect glucose metabolism, whose modifications are only indirectly related to the proliferation status of the tumor. Moreover, the physiological high dependence of normal brain on glucose metabolism results in normally increased fluoro-deoxyglucose uptake, which accounts for the tracer's suboptimal diagnostic performance. Among radiolabeled amino acids, ^{11}C-MET is the most extensively studied with encouraging results, still the short-lived ^{11}C precludes its use in centers without a cyclotron on-site (Kim et al., 2005; Hatakeyama et al., 2008). ^{11}C-thymidine PET is of great interest, since thymidine is the native pyrimidine base used in DNA synthesis, yet suffers from rapid *in vivo* degradation and the limited availability issues of ^{11}C. To overcome these restrictions, ^{18}F-FLT has been

developed as an alternative estimator of the DNA synthesis rate and is currently proving a useful proliferation imaging tracer, correlating well with Ki-67 (Shields et al., 1996; Ullrich et al., 2008).

As in CNS gliomas, ^{18}F-FDG uptake kinetics in meningiomas reflect on glucose metabolism that is only indirectly related to proliferation. In a pilot PET study comprising ^{11}C-MET, tracer uptake succesfully predicted meningioma proliferation (Ki-67) (Iuchi et al., 1999). ^{18}F-FLT also holds plenty of theoretical advantages that remain to be proven in practice.

6. Functional MRI techniques

Conventional radiomorphological imaging —in the form of CT and classic MRI— may face significant limitations in discriminating benign from malignant intracranial space-occupying pathologies, since these modalities basically recognize BBB disruption, mass-effects and edema that can equally accompany both categories of lesions. An answer to these limitations towards the discrimination of neoplastic from non-neoplastic lesions has been attempted by the introduction of functional MRI techniques, namely perfusion MRI and MR spectroscopy (MRS).

Perfusion MRI estimates tumor neovascularity and capillary permeability *in vivo*, by measuring the relative cerebral blood volume (rCBV); higher vascularity usually corresponds to a more aggressive pathology. In the diagnosis between tumor recurrence and radiation injury, perfusion MR holds a role by measuring vascularity within the suspicious brain areas. Since vasculature adjusts perfusion to meet metabolic tissue demands, rich vascularity can be an indirect measure of increased tissue metabolism, with relapsing tumor generally being highly vascular as opposed to radionecrosis (Covarrubias et al., 2004).

Proton MRS is able to depict the metabolic composition of a tissue, by detecting the relative concentrations of several major metabolites such as choline (Cho), creatine (Cr), *N*-acetyl aspartate (NAA) and other macromolecules. NAA is predominantly localized in neurons, Cho is a marker of cell membrane metabolism and Cr reflects energy metabolism. Despite no tumor-specific metabolite has been identified to date, an increased level of Cho with decreased NAA and Cr were proven suggestive of brain tumor (Hollingworth et al., 2006). MRS has been evaluated by several investigators for the differentiation of neoplastic from non-neoplastic intra-axial lesions — such as brain abscess, demyelination, infarct and radiation necrosis — with good results. The Cho/Cr and Cho/NAA ratios tend to increase in cases of tumor reccurence and thus contribute to its differentiation from radiation injury (Ando et al., 2004). This modality has also been evaluated for the non-invasive assessment of glioma aggressiveness, with initial findings associating Cho/Cr and Cho/NAA ratios with proliferative activity (Shimizu et al., 2000; Tamiya et al., 2000).

Diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) constitute modern functional MR techniques, which reflect on the viability and structure of tissues at the cellular level. Their role in differentiating between tumor recurrence and radionecrosis is under study (Hein et al., 2004; Sundgren et al., 2006), while it also remains to be determined whether they can provide findings clearly linkable to glioma proliferative activity.

7. Advantages of ^{99m}Tc-TF for brain SPECT imaging

The ^{99m}Tc-labeled compounds ^{99m}Tc-TF and ^{99m}Tc-MIBI bear certain imaging characteristics that are proven advantageous over ^{201}Tl. The single-photon (γ-ray) emitted by ^{99m}Tc peaks at

140 keV, which is optimal for imaging in the γ-camera, while its higher photon flux results in improved spatial resolution and less radiation burden to the patient. Of note is the excellent availability of ^{99m}Tc in every nuclear medicine department.

^{99m}Tc-TF shares a similar cellular uptake mechanism with ^{99m}Tc-MIBI, yet it mostly localizes within the cytosol, whereas the latter accumulates predominantly in the mitochondria. *In vitro* studies in glioma cell lines substantiated a plausible clinical superiority of ^{99m}Tc-TF over ^{99m}Tc-MIBI in imaging gliomas and meningiomas, largely due to the considerably lesser reliance of its intracellular concentration on cellular MDR expression (P-gp) (Le Jeune et al., 2005). In a recent study we verified *in vivo* this non-dependence of ^{99m}Tc-TF uptake on the glioma MDR phenotype, suggesting that it constitutes an appropriate radiotracer for glioma imaging, although less ideal for identifying P-gp-avid lesions that are likely to respond poorly to chemotherapy (Alexiou et al., 2011).

8. Limitations of ^{99m}Tc-TF brain SPECT

The method's limitations derive mainly from the nature of ^{99m}Tc-TF kinetics in the brain. Although it does not cross the intact BBB, which drastically results in its negligible concentration in the normal brain parenchyma, it physiologically accumulates in the choroid plexuses and the pituitary gland, which are structures normally lacking BBB. Physiological tracer activity comes also from the scalp. This normal uptake may therefore hamper image processing by hindering precise ROI definition for lesions lying adjacently to these anatomical structures and this can prove elaborate even under CT/MRI guidance. In such cases, hybrid SPECT/CT modalities could partially overcome this limitation by providing better spatial tumor localization to co-register with SPECT and also by applying attenuation correction to SPECT image processing and L/N calculation.

Apart from the proximity to areas of normal tracer uptake, location also matters when it comes to lesions sited subtentorially. There are reports suggesting that tumors of the posterior fossa tend to exhibit a lower-than-anticipated tracer uptake that hinders diagnostic accuracy (Barai et al., 2003).

Inherent to the integrity of the BBB is also the fact that ^{99m}Tc-TF has limited ability to penetrate into and characterize metabolically those brain lesions that do not exhibit contrast-enhancement on radiological imaging. Non-enhancement is an indicator of a non-ruptured BBB and is usually observed in low-grade gliomas.

Limitations innate to SPECT instrumentation ought not to be ignored. Spatial resolution is confined to 7.0 mm on ideal situations. In practice this limit usually reaches larger values (8.0-1.0 cm) due to various reasons, which can significantly affect the modality's ability to depict small lesions sized close to that limit.

We should not disregard certain restrictions originating from study design and implementation. Our experience thus far derives from small-scale studies implemented on a single-institution basis and with relatively small numbers of cases. Possible limitations might also emerge from the lack of histological verification in subgroups of the enrolled patients, like in those studies aiming to distinguish tumor recurrence from radionecrosis. Although histology provides the definitive diagnosis, this cannot always be achieved, as in cases of patient denying surgery or when surgical access to the lesion is not feasible. In such instances, a 6-month clinical and radiomorphological close follow-up could provide an acceptable diagnostic alternative, as explained earlier.

9. Conclusion

Radiomorphological imaging of the brain by conventional MRI and CT is of paramount importance in identifying structural abnormalities secondary to the development of space-occupying lesions, especially when those pathologies disrupt the BBB and give rise to contrast enhancement, edema and mass effects. Nevertheless, the true nature of each visible lesion may lie well beyond gross structural patterns, down to the cellular and molecular level. This is where functional metabolic imaging by SPECT, PET and modern MRI techniques come into play and excel.

Histopathology, immunodiagnostic labeling assays to certain cellular antigens and other techniques like flow cytometry applied on excised tissue specimens are considered as the reference standard of diagnosis, of assessing aggressiveness and the likelihood of response to therapy, while also provide an estimate of prognosis. Yet tissue samples are obtained through surgical intervention, which is not always possible for numerous reasons already discussed. Furthermore, regional tissue heterogeneity within brain tumors may result in sampling errors. This underscores the importance of functional brain imaging in providing easily implemented, non-invasive diagnostic and prognostic alternative markers.

Novel MRI techniques like MRS, DWI and DTI, together with certain PET and SPECT radiotracers, show promising results in the non-invasive assessment of tumor grade, proliferative potential, response to therapy and prognostication. In healthcare units without a PET facility, brain SPECT by ^{99m}Tc-TF can render useful metabolic information for newly diagnosed intracranial lesions prior to surgical intervention. Whether pertaining to gliomas or meningiomas, the lesions' grade and proliferation can be efficaciously estimated and credible evaluations may be extracted for their prognosis. The method can also hold a role in the non-invasive diagnostic work-up of hemorrhagic intracerebral lesions, while it certainly has much to offer in differentiating radiation necrosis from brain tumor recurrence in patients previously treated by surgery and adjuvant radio-chemotherapy.

Overall, there is gathering evidence to substantiate the need for larger scale, well-designed, prospective comparative studies between functional MR techniques and PET/SPECT radiotracers like ^{99m}Tc-TF, aiming to increase diagnostic accuracy and establish their clinical role in optimizing treatment decisions and reliably contribute on assessing patient prognosis.

10. References

Ak, I.; Gulbas, Z.; Altinel, F. & Vardareli, E. (2003). Tc-99m MIBI uptake and its relation to the proliferative potential of brain tumors. *Clin Nucl Med*, Vol.28, No.1, (January 2003), pp.29-33, ISSN 03639762

Al-Okaili, R.N.; Krejza, J.; Woo, J.H.; Wolf, R.L.; O'Rourke, D.M.; Judy, K.D.; Poptani, H. & Melhem ER. (2007). Intraaxial brain masses: MR imaging based diagnostic strategy—initial experience. *Radiology*, Vol.243, No.2, (May 2007), pp.539–550, ISSN 0033-8419

Alexiou, G.A.; Bokharhii, J.A.; Kyritsis, A.P.; Polyzoidis, K.S. & Fotopoulos, A.D. (2006). Tc-99m Tetrofosmin SPECT for the differentiation of a cerebellar hemorrhage

mimicking a brain metastasis from a renal cell carcinoma. *J Neurooncol*, Vol.78, No.2, (March 2006), pp.207-208, ISSN 0167-594X

Alexiou, G.A.; Fotopoulos, A.D., Papadopoulos, A.; Kyritsis, A.P.; Polyzoidis, K.S. & Tsiouris, S. (2007). Evaluation of brain tumor recurrence by (99m)Tc-tetrofosmin SPECT: a prospective pilot study. *Ann Nucl Med*, Vol.21, No.5, (July 2007), pp.293-298, ISSN 0914-7187

Alexiou, G.A.; Tsiouris, S.; Goussia, A.; Papadopoulos, A.; Kyritsis, A.P.; Polyzoidis, K.S. & Fotopoulos, A.D. (2008). Evaluation of glioma proliferation by ^{99m}Tc-Tetrofosmin. *NeuroOncol*, Vol.10, No.1, (February 2008), pp.104-105, ISSN 1522-8517

Alexiou, G.A.; Vartholomatos, G.; Tsiouris, S.; Papadopoulos, A.; Kyritsis, A.P.; Polyzoidis, K.S.; Voulgaris, S. & Fotopoulos, A.D. (2008). Evaluation of meningioma aggressiveness by (99m)Tc-Tetrofosmin SPECT. *Clin Neurol Neurosurg*, Vol.110, No.7, (July 2008), pp.645-648, ISSN 0303-8467

Alexiou, G.A.; Tsiouris, S.; Kyritsis, A.P.; Fotakopoulos, G. ; Goussia, A.; Voulgaris, S. & Fotopoulos, A.D. (2010). The Value of ^{99m}Tc-Tetrofosmin Brain SPECT in Predicting Survival in Patients with Glioblastoma Multiforme. *J Nucl Med*, Vol.51, No.12, (December 2010), pp.1923-1926, ISSN 0161-5505

Alexiou, G.A.; Goussia, A.; Kyritsis, A.P.; Tsiouris, S.; Ntoulia, A.; Malamou-Mitsi, V.; Voulgaris, S. & Fotopoulos, A.D. (2011). Influence of Glioma's Multidrug Resistance Phenotype on (99m)Tc-Tetrofosmin Uptake. *Mol Imaging Biol*, Vol.13, No.2, (April 2011), pp.348-351, ISSN 1536-1632

Ando, K.; Ishikura, R.; Nagami, Y.; Morikawa, T.; Takada, Y.; Ikeda, J.; Nakao, N.; Matsumoto, T. & Arita, N. (2004). Usefulness of Cho/Cr ratio in protonMR spectroscopy for differentiating residual/recurrent glioma from non-neoplastic lesions. *Nippon Igaku Hoshasen Gakkai Zasshi*, Vol.64, No.3, (March 2004), pp.121–126, ISSN 0048-0428

Barai, S.; Bandopadhayaya, G.P.; Julka, P.K.; Haloi, A.K.; Seith, A. & Malhotra A. (2003). Evaluation of single photon emission computerised tomography (SPECT) using Tc99m-tetrofosmin as a diagnostic modality for recurrent posterior fossa tumours. *J Postgrad Med*, Vol.49, No.4, (October-December 2003), pp.316-320, ISSN 0022-3859

Barai, S.; Bandopadhayaya, G.P.; Julka, P.K.; Kale, S.S.; Malhotra, A.; Haloi, A.K.; Seith, A. & Gopendro Sing, N. (2004). Evaluation of ^{99m}Tc-L-methionine brain SPECT for detection of recurrent brain tumor: a pilot study with radiological and pathological correlation. *Acta Radiol*, Vol.45, No.6, (October 2004), pp.649-657, ISSN 0284-1851

Beauchesne, P.; Pedeux, R.; Boniol, M. & Soler, C. (2004). ^{99m}Tc-sestamibi brain SPECT after chemoradiotherapy is prognostic of survival in patients with high-grade glioma. *J Nucl Med*, Vol.45, No.3, (March 2004), pp.409-413, ISSN 0161-5505

Byrne, T.N. (1994). Imaging of gliomas. *Semin Oncol*, Vol.21, No.2, (April 1994), pp.162-171, ISSN 0093-7754

Chen, W.; Cloughesy, T.; Kamdar, N.; Satyamurthy, N.; Bergsneider, M.; Liau, L.; Mischel, P.; Czernin, J.; Phelps, M.E. & Silverman, D.H. (2005). Imaging proliferation in

brain tumors with ^{18}F-FLT PET: comparison with ^{18}F-FDG. *J Nucl Med*, Vol.46, No.6, (June 2005), pp.945-952, ISSN 0161-5505

Chen, W.; Silverman, D.H.; Delaloye, S.; Czernin, J.; Kamdar, N.; Pope, W.; Satyamurthy, N.; Schiepers, C. & Cloughesy, T. (2006). ^{18}F-FDOPA PET imaging of brain tumors: comparison study with ^{18}F-FDG PET and evaluation of diagnostic accuracy. *J Nucl Med*, Vol.47, No.6, (June 2006), pp.904-911, ISSN 0161-5505

Choi, J.Y.; Kim, S.E.; Shin, H.J.; Kim, B.T. & Kim, J.H. (2000). Brain tumor imaging with ^{99m}Tc-tetrofosmin: comparison with ^{201}Tl, ^{99m}Tc-MIBI, and ^{18}F-fluorodeoxyglucose. *J Neurooncol*, Vol.46, No.1, (January 2000), pp.63-70, ISSN 0167-594X

Covarrubias, D.J.; Rosen, B.R. & Lev, M.H. (2004). Dynamic magnetic resonance perfusion imaging of brain tumors. *Oncologist*, Vol.9, No.9, (May 2004), pp.528-537, ISSN 1083-7159

DeAngelis, L.M. (2001). Brain tumors. *N Engl J Med*, Vol.344, No.2, (January 2001), pp.114-123, ISSN 0028-4793

Denoyer, D.; Perek, N.; Le Jeune, N.; Cornillon, J. & Dubois, F. (2005). Correlation between ^{99m}Tc-(V)-DMSA uptake and constitutive level of phosphorylated focal adhesion kinase in an in vitro model of cancer cell lines. *Eur J Nucl Med Mol Imaging*, Vol.32, No.7, (July 2005), pp.820-827, ISSN 1619-7070

Di Chiro, G.; Oldfield, E.; Wright, D.C.; De Michele, D.; Katz, D.A.; Patronas, N.J.; Doppman, J.L.; Larson, S.M.; Ito, M. & Kufta, C.V. (1988). Cerebral necrosis after radiotherapy and/or intraarterial chemotherapy for brain tumors: PET and neuropathologic studies. *AJR Am J Roentgenol*, Vol.150, No.1, (January 1988), pp.189-197, ISSN 0361-803X

Fotopoulos, A.D., Alexiou, G.A.; Goussia, A.; Papadopoulos, A.; Kyritsis, A.P.; Polyzoidis, K.S.; Voulgaris, S. & Tsiouris, S. (2008). (99m)Tc-Tetrofosmin brain SPECT in the assessment of meningiomas – correlation with histological grade and proliferation index. *J Neurooncol*, Vol.89, No.2, (September 2008), pp.225-230, ISSN 0167-594X

Fotopoulos, A.D.; Kyritsis, A.P.; Tsiouris, S.; Al-Boucharali, J.; Papadopoulos, A.; Voulgaris, S. & Alexiou, G.A. (2011). Characterization of intracranial space-occupying lesions by ^{99}(m)Tc-Tetrofosmin SPECT. *J Neurooncol*, Vol.101, No.1, (January 2011), pp.83-89, ISSN 0167-594X

Galldiks, N.; Kracht, L.W.; Berthold, F.; Miletic, H.; Klein, J.C.; Herholz, K.; Jacobs, A.H. & Heiss, W.D. (2010). [(11)C]-L: -Methionine positron emission tomography in the management of children and young adults with brain tumors. *J Neurooncol*, Vol.96, No.2, (January 2010), pp.231-239, ISSN 0167-594X

Garcia, R.; Bueno, A. & Castanon, S. (1997). Study of the DNA content by flow cytometry and proliferation in 281 brain tumors. *Oncology*, Vol.54, No.2, (March-April 1997), pp.112-117, ISSN 0890-9091

Gómez-Río, M.; Rodríguez-Fernández, A.; Ramos-Font, C.; López-Ramírez, E. & Llamas-Elvira, J.M. (2008). Diagnostic accuracy of ^{201}Thallium-SPECT and ^{18}F-FDG-PET in the clinical assessment of glioma recurrence. *Eur J Nucl Med Mol Imaging*, Vol.35, No.5, (May 2008), pp.966-975, ISSN 16197070

Gungor, F.; Bezircioglu, H.; Guvenç, G.; Tezcan, M.; Yildiz, A.; Uluc, E. & Isisag, A. (2000). Correlation of thallium-201 uptake with proliferating cell nuclear antigen in brain tumours. *Nucl Med Commun*, Vol.21, No.9, (September 2000), pp.803-810, ISSN 01433636

Hatakeyama, T.; Kawai, N.; Nishiyama, Y.; Yamamoto, Y.; Sasakawa, Y.; Ichikawa, T. & Tamiya, T. (2008). ^{11}C-methionine (MET) and ^{18}F-fluorothymidine (FLT) PET in patients with newly diagnosed glioma. *Eur J Nucl Med Mol Imaging*, Vol.35, No.11, (November 2008), pp.2009-2017, ISSN 16197070

Hein, P.A.; Eskey, C.J.; Dunn, J.F. & Hug, E.B. (2004). Diffusion-weighted imaging in the follow-up of treated high-grade gliomas: tumor recurrence versus radiation injury. *AJNR Am J Neuroradiol*, Vol.25, No.2, (February 2004), pp.201-209, ISSN 01956108

Hollingworth, W.; Medina, S.; Lenkinski, R.E.; Shibata, D.K.; Bernal, B.; Zurakowski, D.; Comstock, B. & Jarvik, J.G. (2006). A Systematic Literature Review of Magnetic Resonance Spectroscopy for the Characterization of Brain Tumors. *AJNR Am J Neuroradiol*, Vol.27, No.7, (August 2006), pp.1404-1411, ISSN 01956108

Ishibashi, M.; Taguchi, A.; Sugita, Y.; Morita, S.; Kawamura, S.; Umezaki, N.; Shigemori, M. & Hayabuchi, N. (1995). Thallium-201 in brain tumors: relationship between tumor cell activity in astrocytic tumor and proliferating cell nuclear antigen. *J Nucl Med*, Vol.36, No.12, (December 1996), pp.2201-2206, ISSN 01615505

Iuchi, T.; Iwadate, Y.; Namba, H.; Osato, K.; Saeki, N.; Yamaura, A. & Uchida, Y. (1999). Glucose and methionine uptake and proliferative activity in meningiomas. *Neurol Res*, Vol.21, No.7, (October 1999), pp.640-644, ISSN 01616412

Jinnouchi, S.; Hoshi, H.; Ohnishi, T.; Futami, S.; Nagamachi, S.; Watanabe, K.; Ueda, T. & Wakisaka, S. (1993). Thallium-201 SPECT for predicting histological types of meningiomas. *J Nucl Med*, Vol.34, No.12, (December 1993), pp.2091-2094, ISSN 01615505

Kahn, D.; Follett, K.A.; Bushnell, D.L.; Nathan, M.A.; Piper, J.G.; Madsen, M. & Kirchner, P.T. (1994). Diagnosis of recurrent brain tumor: value of ^{201}Tl SPECT vs ^{18}F-fluorodeoxyglucose PET. *AJR Am J Roentgenol*, Vol.163, No.6, (Decenmber 1994), pp.1459-1465, ISSN 0361803X

Kayaselcuk, F.; Zorludemir, S.; Bal, N.; Erdogan, B.; Erdogan, S. & Erman, T. (2004). The expression of survivin and Ki-67 in meningiomas: correlation with grade and clinical outcome. *J Neurooncol*, Vol.67, No.1-2, (March-April 2004), pp.209-214, ISSN 0167594X

Kim, S.; Chung, J.K.; Im, S.H.; Jeong, J.M.; Lee, D.S.; Kim, D.G.; Jung, H.W. & Lee, M.C. (2005). ^{11}C-methionine PET as a prognostic marker in patients with glioma: comparison with ^{18}F-FDG PET. *Eur J Nucl Med Mol Imaging*, Vol.32, No.1, (January 2005), pp.52-59, ISSN 16197070

Kinuya, K.; Ohashi, M.; Itoh, S.; Yamamoto, K.; Sakai, S.; Kakuda, K.; Nobata, K.; Kato, N.; Terahara, S. & Taki, S. (2002). Differential diagnosis in patients with ring-like thallium-201 uptake in brain SPECT. *Ann Nucl Med*, Vol.16, No.6, (September 2002), pp.417-421, ISSN 09147187

Kuwert, T.; Probst-Cousin, S.; Woesler, B.; Morgenroth, C.; Lerch, H.; Matheja, P.; Palkovic, S.; Schäfers, M.; Wassmann, H.; Gullotta, F. & Schober, O. (1997). Iodine-123-alpha-methyl tyrosine in gliomas: correlation with cellular density and proliferative activity. *J Nucl Med*, Vol.38, No.10, (October 1997), pp.1551-1555, ISSN 01615505

Kwee, S.A.; Ko, J.P.; Jiang, C.S.; Watters, M.R. & Coel, M.N. (2007). Solitary brain lesions enhancing at MR imaging: evaluation with fluorine 18 fluorocholine PET. *Radiology*, Vol.244, No.2, (August 2007), pp.557-565, ISSN 00338419

Lacroix, M.; Abi-Said, D.; Fourney, D.R.; Gokaslan, Z.L.; Shi, W.; DeMonte. F.; Lang, F.F.; McCutcheon, I.E.; Hassenbusch, S.J.; Holland, E.; Hess, K.; Michael, C.; Miller, D. & Sawaya, R. (2001). A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*, Vol.95, No.2, (August 2001), pp.190–198, ISSN 0022308

Lamszus, K. (2004). Meningioma pathology, genetics, and biology. *J Neuropathol Exp Neurol*, Vol.63, No.4, (April 2004), pp.275-286, ISSN 0022-3069

Le Jeune, N.; Perek, N.; Denoyer, D. & Dubois, F. (2005). Study of monoglutathionyl conjugates TC-99M-sestamibi and TC-99M-tetrofosmin transport mediated by the multidrug resistance-associated protein isoform 1 in glioma cells. *Cancer Biother Radiopharm*, Vol.20, No.3, (June 2005), pp.249-259, ISSN 10849785

Liu, Y.; Shete, S.; Etzel, C.J.; Scheurer, M.; Alexiou, G.; Armstrong, G.; Tsavachidis, S.; Liang, F.W.; Gilbert, M.; Aldape, K.; Armstrong, T.; Houlston, R.; Hosking, F.; Robertson, L.; Xiao, Y.; Wiencke, J.; Wrensch, M.; Andersson, U.; Melin, B.S. & Bondy, M. (2010). Polymorphisms of LIG4, BTBD2, HMGA2, and RTEL1 genes involved in the double-strand break repair pathway predict glioblastoma survival. *J Clin Oncol*, Vol.28, No.14, (May 2010), pp.2467-2474, ISSN 0732-183X

Marks, J.E. & Wong, J. (1985). The risk of cerebral radionecrosis in relation to dose, time and fractionation: a followup study. *Prog Exp Tumor Res*, Vol.29, No.1, (January 1985), pp.210–218, ISSN 00796263

McKeever, P.E.; Ross, D.A.; Strawderman, M.S.; Brunberg, J.A.; Greenberg, H.S. & Junck, L. (1997). A comparison of the predictive power for survival in gliomas provided by MIB-1, bromodeoxyuridine and proliferating cell nuclear antigen with histopathologic and clinical parameters. *J Neuropathol Exp Neurol*, Vol.56, No.7, (July 1997), pp.798–805, ISSN 00223069

Minutoli, F.; Angileri, F.F.; Conti, A.; Herberg, A.; Aricò, D.; Baldari, S.; Cardali, S.; de Divitiis, O.; Germanò, A. & Baldari, S. (2005). Timing of examination affects reliability of ^{99m}Tc-methoxyisobutylisonitrile SPECT in distinguishing neoplastic from nonneoplastic brain hematomas. *J Nucl Med*, Vol.46, No.4, (April 2005), pp.574-579, ISSN 01615505

Nagamachi, S.; Jinnouchi, S.; Nabeshima, K.; Nishii, R.; Flores, L. 2nd; Kodama, T.; Kawai, K.; Tamura, S.; Yokogami, K.; Samejima, T. & Wakisaka, S. (2001). The correlation between ^{99m}Tc-MIBI uptake and MIB-1 as a nuclear proliferation marker in glioma—a comparative study with ^{201}Tl. *Neuroradiology*, Vol.43, No.12, (December 2001), pp.1023-1030, ISSN 00283940

Oriuchi, N.; Tamura, M.; Shibazaki, T.; Ohye, C.; Watanabe, N.; Tateno, M.; Tomiyoshi, K.; Hirano, T.; Inoue, T. & Endo, K. (1993). Clinical evaluation of thallium-201 SPECT

in supratentorial gliomas: relationship to histologic grade, prognosis and proliferative activities. *J Nucl Med*, Vol.34, No.12, (December 1993), pp.2085-2089, ISSN 01615505

Pauleit, D.; Stoffels, G.; Bachofner, A.; Floeth, F.W.; Sabel, M.; Herzog, H.; Tellmann, L.; Jansen, P.; Reifenberger, G.; Hamacher, K.; Coenen, H.H. & Langen, K.J. (2009). Comparison of (18)F-FET and (18)F-FDG PET in brain tumors. *Nucl Med Biol*, Vol.36, No.7, (October 2009), pp.779-787, ISSN 09698051

Pöpperl, G.; Götz, C.; Rachinger, W.; Gildehaus, F.J.; Tonn, J.C. & Tatsch, K. (2004). Value of O-(2-[^{18}F]fluoroethyl)- L-tyrosine PET for the diagnosis of recurrent glioma. *Eur J Nucl Med Mol Imaging*, Vol.31, No.11, (November 2004), pp.1464-1470, ISSN 16197070

Ricci, P.E.; Karis, J.P.; Heiserman, J.E.; Fram, E.K.; Bice, A.N. & Drayer, B.P. (1998). Differentiating recurrent tumor from radiation necrosis: time for re-evaluation of positron emission tomography? *AJNR Am J Neuroradiol*, Vol.19, No.3, (March 1998), pp.407-413, ISSN 01956108

Samnick, S.; Bader, J.B.; Hellwig, D.; Moringlane, J.R.; Alexander, C.; Romeike, B.F.; Feiden, W. & Kirsch, C.M. (2002). Clinical value of iodine-123-alpha-methyl-L-tyrosine single-photon emission tomography in the differential diagnosis of recurrent brain tumor in patients pretreated for glioma at follow-up. *J Clin Oncol*, Vol.20, No.15, (January 2002), pp.396-404, ISSN 0732183X

Scott, J.N.; Rewcastle, N.B.; Brasher, P.M.; Fulton, D.; MacKinnon, J.A.; Hamilton, M.; Cairncross, J.G. & Forsyth, P. (1999). Which glioblastoma multiforme patient will become a long-term survivor? A population-based study. *Ann Neurol*, Vol.46, No.2, (August 1999), pp.183-188, ISSN 03645134

Shields, A.F.; Grierson, J.R.; Kozawa, S.M. & Zheng, M. (1996). Development of labeled thymidine analogs for imaging tumor proliferation. *Nucl Med Biol*, Vol.23, No.1, (January 1996), pp.17–22, ISSN 09698051

Shimizu, H.; Kumabe, T.; Shirane, R. & Yoshimoto, T. (2000). Correlation between choline level measured by proton MR spectroscopy and Ki-67 labeling index in gliomas. *AJNR Am J Neuroradiol*, Vol.21, No.4, (April 2000), pp.659-665, ISSN 0195-6108

Soler, C.; Beauchesne, P.; Maatougui, K.; Schmitt, T.; Barral, F.G.; Michel, D.; Dubois, F. & Brunon, J. (1998). Technetium-99m sestamibi brain single-photon emission tomography for detection of recurrent gliomas after radiation therapy. *Eur J Nucl Med*, Vol.25, No.12, (December 1998), pp.1649-1657, ISSN 16197070

Soricelli, A.; Cuocolo, A.; Varrone, A.; Discepolo, A.; Tedeschi, E.; Mainenti, P.P.; Grivet-Fojaja, M.R.; Covelli, E.M.; Postiglione, A. & Salvatore, M. (1998). Technetium-99m-tetrofosmin uptake in brain tumors by SPECT: comparison with thallium-201 imaging. *J Nucl Med*, Vol.39, No.5, (May 1998), pp.802-806, ISSN 01615505

Staffen, W.; Hondl, N.; Trinka, E.; Iglseder, B.; Unterrainer, J. & Ladurner, G. (1998). Clinical relevance of ^{201}Tl-chloride SPET in the differential diagnosis of brain tumours. *Nucl Med Commun*, Vol.19, No.4, (April 1998), pp.335-340, ISSN 01433636

Stupp, R.; Mason, W.P.; van den Bent, M.J.; Weller, M.; Fisher, B.; Taphoorn, M.J.; Belanger, K.; Brandes, A.A.; Marosi, C.; Bogdahn, U.; Curschmann, J.; Janzer, R.C.; Ludwin, S.K.; Gorlia, T.; Allgeier, A.; Lacombe, D.; Cairncross, J.G.; Eisenhauer, E.; Mirimanoff, R.O.; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups & National Cancer Institute of Canada Clinical Trials Group. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New Engl J Med*, Vol.352, No.10, (March 2005), pp.987-996, ISSN 00284793

Sundgren, P.C.; Fan, X.; Weybright, P.; Welsh, R.C.; Carlos, R.C.; Petrou, M.; McKeever, P.E. & Chenevert, T.L. (2006). Differentiation of recurrent brain tumor versus radiation injury using diffusion tensor imaging in patients with new contrast-enhancing lesions. *Magn Reson Imaging*, Vol.24, No.9, (November 2006), pp.1131-1142, ISSN 0730-725X

Tamiya, T.; Kinoshita, K.; Ono, Y.; Matsumoto, K.; Furuta, T. & Ohmoto, T. (2000). Proton magnetic resonance spectroscopy reflects cellular proliferative activity in astrocytomas. *Neuroradiology*, Vol.42, No.5, (May 2000), pp.333-338, ISSN 00283940

Tedeschi, E.; Soricelli, A.; Brunetti, A.; Romano, M.; Bucciero, A.; Iaconetta, G.; Alfieri, A.; Postiglione, A. & Salvatore, M. (1996). Different thallium-201 single-photon emission tomographic patterns in benign and aggressive meningiomas. *Eur J Nucl Med*, Vol.23, No.11, (November 1996), pp.1478-1484, ISSN 16197070

Tsiouris, S.; Pirmettis, I.; Chatzipanagiotou, T.; Ptohis, N. & Papantoniou, V. (2007). Pentavalent technetium-99m dimercaptosuccinic acid [^{99m}Tc-(V)DMSA] brain scintitomography--a plausible non-invasive depicter of glioblastoma proliferation and therapy response. *J Neurooncol*, Vol.85, No.3, (December 2007), pp.291-295, ISSN 0167594X

Ullrich, R.; Backes, H.; Li, H.; Kracht, L.; Miletic, H.; Kesper, K.; Neumaier, B.; Heiss, W.D.; Wienhard, K. & Jacobs, A.H. (2008). Glioma proliferation as assessed by 3'-fluoro-3'-deoxy-L-thymidine positron emission tomography in patients with newly diagnosed high-grade glioma. *Clin Cancer Res*, Vol.14, No.7, (April 2008), pp.2049-2055, ISSN 1078-0432

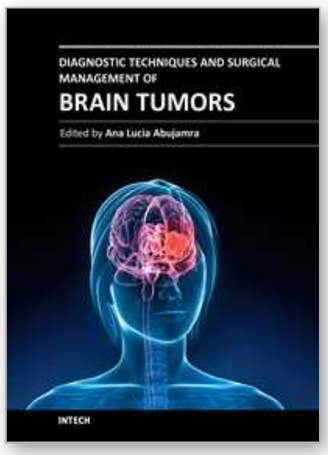
Van Laere, K.; Ceyssens, S.; Van Calenbergh, F.; de Groot, T.; Menten, J.; Flamen, P.; Bormans, G. & Mortelmans, L. (2005). Direct comparison of ^{18}F-FDG and ^{11}C-methionine PET in suspected recurrence of glioma: sensitivity, inter-observer variability and prognostic value. *Eur J Nucl Med Mol Imaging*, Vol.32, No.1, (January 2005), pp.39-51, ISSN 16197070

Vos, M.J.; Tony, B.N.; Hoekstra, O.S.; Postma, T.J.; Heimans, J.J. & Hooft, L. (2007). Systematic review of the diagnostic accuracy of ^{201}Tl single photon emission computed tomography in the detection of recurrent glioma. *Nucl Med Commun*, Vol.28, No.6, (June 2007), pp.431-439, ISSN 01433636

Weber, W.A.; Dick, S.; Reidl, G.; Dzewas, B.; Busch, R.; Feldmann, H.J.; Molls, M.; Lumenta, C.B.; Schwaiger, M. & Grosu, A.L. (2001). Correlation between postoperative 3-[(123)I]iodo-L-alpha-methyltyrosine uptake and survival in patients with gliomas. *J Nucl Med*, Vol.42, No.8, (August 2001), pp.1144-1150, ISSN 01615505

Whittle, I.R.; Smith, C.; Navoo, P. & Collie, D. (2004). Meningiomas. *Lancet*, Vol.363, No. 9431, (May 2004), pp.1535-1543, ISSN 01406736

Xiangsong, Z.; Changhong, L.; Weian, C. & Dong, Z. (2006). PET Imaging of cerebral astrocytoma with ^{13}N-ammonia. *J Neurooncol*, Vol.78, No.2, (June 2006), pp.145-151, ISSN 0167594X



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